UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

OREXO AB, Plaintiff, v. MYLAN PHARMACEUTICALS INC. and MYLAN INC., Defendants.	Civil Action No. 3:11–cv–3788–FLW–LHG Hon. Freda L. Wolfson, U.S.D.J. Hon. Lois H. Goodman, U.S.M.J. Document Filed Electronically

DEFENDANTS' RESPONDING CLAIM CONSTRUCTION BRIEF

Arnold B. Calmann (abc@saiber.com)
Jeffrey Soos (js@saiber.com)
Katherine A. Escanlar (kae@saiber.com)
SAIBER LLC
One Gateway Center, 10th Floor
Newark, New Jersey 07102-5311
973-622-3333
973-286-2465 (facsimile)

Douglass C. Hochstetler
(DHochstetler@KelleyDrye.com)
Constantine Koutsoubas
(CKoutsoubas@KelleyDrye.com)
KELLEY DRYE & WARREN LLP
333 West Wacker Drive
26th Floor
Chicago, IL 60606
312-857-7070
312-857-7095 (facsimile)

Beth D. Jacob (BJacob@KelleyDrye.com)
Clifford Katz (CKatz@KelleyDrye.com)
Sung W. Kim (SuKim@KelleyDrye.com)
KELLEY DRYE & WARREN LLP
101 Park Avenue
New York, NY 10178
212-808-7800
212-808-7897 (facsimile)

Attorneys for Defendants/Counterclaim Plaintiffs Mylan Pharmaceuticals Inc. and Mylan Inc.

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INTRODUCTION

There is a unifying theme connecting the four claim terms addressed in this brief. The theme is that patent claims are most reliably interpreted when the interpretation is based on the patent itself and what the patent applicants told the patent examiner and the public in the course of obtaining their patent.

For the first claim term, "bioadhesion and/or mucoadhesion promoting agent," there was not even a hint in the patent or the prosecution history that cross-linked polyvinylpyrrolidone ("cross-linked PVP") was such an agent. Indeed, an argument that the applicants offered in an effort to obtain allowance of the patent claims pre-supposed that cross-linked PVP was not a "bioadhesion and/or mucoadhesion promoting agent," because the argument would have been false were cross-linked PVP such an agent.

The second term, "essentially water-free," is found in both U.S. Patent No. 6,761,910[1] ("'910 patent") and the prior art European patent cited in the '910 patent, EP 0 324 725[2] (referred to herein as "Nyström"). The '910 patent describes its invention as involving the application of the ordered mixture technology disclosed in Nyström to sublingual dosage forms. The '910 patent never once suggests that Nyström's requirement that the ordered mixture be "essentially water-free" differed from the way the '910 patent (which shared C. Nyström as an inventor) likewise required that the ordered mixture be "essentially water-free." Inasmuch as there is no dispute that "essentially water-free" in the Nyström reference meant that water was intended to be excluded from the ordered mixture, the same interpretation to the identical phrase should be given to "essentially water-free" in the '910 patent.

Third, patent claim 1 expressly states that its "ordered mixture" contains, among other things, microparticles of active agent. The patent specification, when read in its entirety, supports this straightforward reading. Accordingly, Orexo's argument that the ordered mixture need not

[1] Declaration of Constantine Koutsoubas in Supp. of Defendants' Opening Claim Construction Brief ("Koutsoubas Opening Decl."), Ex. 1, Oct. 5, 2012, ECF No. 95-5.

[2] Koutsoubas Opening Decl., Ex. 3, ECF No. 95-5.

contain the active agent—when the entire purpose of the '910 patent is to deliver the active agent sublingually to the patient—is squarely inconsistent with the entirety of the '910 patent.

Finally, the interrelated terms "effective amount" and "treatment" have real meaning—contrary to Orexo's proferred construction. The meaning supported in the patent specification and claims is that an "effective amount" is an amount sufficient to treat an acute disorder, where "treat," in turn, is directed to "control" of the disorder. Orexo's alternate proposed construction for "treatment," which simply requires the "application of medicines," would impermissibly read the word "effective" out of the claim term "effective amount" because any amount of active agent, however negligible, might be argued to constitute an "application of medicines."

Accordingly, Mylan respectfully requests that the Court adopt Mylan's proposed constructions.

DISCUSSION

I. THERE IS NO EVIDENCE THAT, AT THE TIME OF APPLICATION, A PERSON OF ORDINARY SKILL WOULD HAVE CONSIDERED CROSS-LINKED PVP AS A MUCOADHESIVE

As pointed out in our opening brief, it is the intrinsic evidence of claim meaning (the patent itself and its history of prosecution in the Patent and Trademark Office, "PTO") that is the more reliable indicator of claim meaning. *See generally Phillips v. AWH Corp*., 415 F.3d 1303, 1311–24 (Fed. Cir. 2005) (en banc). "The meaning of patent terms depends on the usage of those terms in context by one of skill in the art *at the time of application*." *Middleton, Inc. v. Minnesota Mining & Mfg. Co.*, 311 F.3d 1384, 1389 (Fed. Cir. 2002) (emphasis added).

Orexo's evidence for cross-linked PVP being a "bioadhesion and/or mucoadhesion promoting agent" ("mucoadhesive") for the purposes of the patent is entirely extrinsic, and post-dates the filing of the '910 patent.[3]

[3] Mylan also contests that these articles show that cross-linked PVP is a mucoadhesive. For example, Bredenberg contains evidence that (at most) points both ways as to whether cross-linked PVP can function as a mucoadhesive in an ordered mixture. The deposition testimony of Orexo's expert on this point includes admissions that Bredenberg does not contain data that would allow the expert to answer critical questions about cross-linked PVP as a mucoadhesive in

More in line with the intrinsic evidence that a person of skill would *not* consider cross-linked PVP to be a mucoadhesive, was the admission of Orexo's expert that he does not recall even once in his more than 100 published papers on mucoadhesives, describing cross-linked PVP as a mucoadhesive. Peppas Dep. 30:15–20. This tracks the view of Mylan's expert, which was ably summarized by none other than Orexo's own counsel: "I understand that you're—you're strong on your opinion that cross-linked PVP is not covered by the claims of the '910 patent." Deposition of Edmund J. Elder, Jr. ("Elder Dep.") 89:8–10, Nov. 14, 2012 (attached hereto as Koutsoubas Suppl. Decl., Ex. 2).

Thus, substantial extrinsic evidence is in line with the patent application itself, which listed MCC both as a mucoadhesive and as a disintegrant, but cross-linked PVP *only* as the latter. Thus at the time of application filing, the application itself taught cross-linked PVP to be only a disintegrant. *See, e.g.*, Defs.' Opening Claim Construction Br. at 5–7, Oct. 5, 2012, ECF No. 95 ("Mylan's Opening Br.").

As discussed in our opening brief, another element of intrinsic evidence—the prior art Nyström[4] reference—disclosed the combination of an ordered mixture with MCC and cross-linked PVP.[5] Orexo represented to the examiner that Nyström did not disclose a combination of ordered mixtures and mucoadhesive agents. Koutsoubas Opening Decl., Ex. 2 at

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an ordered mixture. Deposition of Nicholas Peppas ("Peppas Dep.") 102:4–139:17, Nov. 29, 2012 (attached hereto as Supplemental Declaration of Constantine Koutsoubas in Supp. of Defendants' Responding Claim Construction Brief ("Koutsoubas Suppl. Decl."), Ex. 1, Dec. 7, 2012). The article states that when cross-linked PVP was included in an ordered mixture, as Orexo contends it must under its construction of "ordered mixture," "[d]espite the high surface area coverage of the carrier particles (1.5), the concentration of Kollidon CLM [cross-linked PVP] was too low to increase ($p>0.1$) the bioadhesive capability of DCP." Declaration of Dr. Nicholas A. Peppas on Claim Construction("Peppas Decl."), Ex. 15 at ORM_00001349, Oct. 5, 2012, ECF No. 96-1 (*exhibit available at* ECF No. 97-1).

[4] *See Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583 (Fed. Cir. 1996) ("Included within an analysis of the file history may be an examination of the prior art cited therein.")

[5] Orexo's expert agrees with Mylan's expert that Nyström discloses cross-linked PVP. *See* Peppas Decl. ¶ 138.2.

ORM_00000181 (Feb. 23, 2003 Amendment, p. 6). The examiner had rejected the pending patent claims, noting in the rejection that Nyström specifically disclosed both what the '910 patent called a mucoadhesive agent (namely, MCC) and a disintegrant (namely cross-linked PVP). *Id.* at ORM_00000161 (Sept. 26, 2002 Office Action, p. 6). To overcome the rejection, Orexo represented that Nyström did not disclose a combination of ordered mixtures and mucoadhesive agents:

> *Moreover, applicants note that NYSTROM fails to mention muco- or bioadhesive components. In fact, NYSTROM fails to disclose or suggest a combination of ordered mixtures and mucoadhesive agents.* Moreover, applicants note that one of ordinary skill in the art would appreciate that microcrystalline cellulose does not exhibit bio/mucoadhesive properties. While it is true that this is stated in the specification and claims, applicants have amended the claims and specification to correct this obvious error.

Id. at ORM_00000181 (Feb. 23, 2003 Amendment, p. 6) (emphasis added).

Orexo's explanation for the italicized representation does not withstand scrutiny. Orexo offers the post-hoc rationalization that "[s]killed persons would understand that applicant's statement that 'Nyström fails to mention muco- or bioadhesive components' and 'Nyström fails to disclose or suggest a combination of ordered mixtures and mucoadhesive agents' is based on the fact that Nyström does not address whether any of the materials listed therein exhibited bioadhesive properties." Orexo AB's Opening *Markman* Submission ("OB") at 12, Oct. 5, 2012, ECF No. 96. There are at least two problems with this revisionist interpretation insofar as cross-linked PVP is concerned.

First, Orexo's argument hints at the premise that it is significant whether Nyström used words like "bioadhesive" or "mucoadhesive." But, if the absence of those terms were relevant, there would have been no need for Orexo to include the two non-italicized sentences in the above-quoted excerpt, because there is no dispute that Nyström does not expressly or implicitly *call* MCC a "bioadhesive" or "mucoadhesive." Those two added sentences reflect that Orexo was actually distinguishing Nyström based on Orexo's assertion that "[i]n fact, NYSTROM fails

to disclose or suggest a combination of ordered mixtures and mucoadhesive agents"—not on the legally insufficient ground Nyström did not use a word like "mucoadhesive" to describe MCC.

An instructive case is *In re Kao*, 639 F.3d 1057 (Fed. Cir. 2011), which involved obviousness rejections of multiple patent applications relating to a drug called oxymorphone. In reviewing the rejection of one application where patentability of the claim depended on a correlation between two tests, the Federal Circuit summarized the principle applicable there and here (the emphasis is the Federal Circuit's): "Thus, while it matters not whether the hypothetical skilled artisan would have *appreciated* the 'correlation' at issue here, it matters greatly whether anything the skilled artisan would be prompted by the prior art to do is *in fact* within the scope of the pending claim." *Id.* at 1066.[6]

The same principle applies here. When the examiner made his rejection, it mattered not whether the hypothetical skilled artisan would have *appreciated* that MCC was a mucoadhesive; rather it mattered greatly whether the skilled artisan would have been prompted by the prior art Nyström reference to combine an ordered mixture with what was *in fact* a mucoadhesive as stated in the pending claim.

The *Kao* court's application of this principle to another application is also instructive. This other application claimed that oxymorphone gave rise to a favorable "food effect." The claim had been rejected by the PTO as obvious in view of a prior art reference by Maloney,

[6] The applicable facts in *Kao* are a bit complicated. The claimed invention required, *inter alia*, that 15–50% of the oxymorphone dissolve in the first hour of a test called the "Paddle Method." *Id.* at 1061–62. A prior art reference disclosed values from a different dissolution test, the "Basket Method." *Id.* at 1062. The PTO Board rejected the claim on the basis that one could correlate the Basket Method dissolution results to give the claimed Paddle Method results. *Id.* at 1062–63. The Federal Circuit vacated the rejection because the PTO Board lacked evidence for its conclusion of a correlation between the two test methods, and thus had failed to establish that the prior art *in fact* disclosed a composition that would dissolve 15–50% of the oxymorphone in the first hour using the Paddle Method. *Id.* at 1067. The Federal Circuit, in the excerpt quoted in the text, pointed out it was irrelevant whether a person skilled in the art would have understood if and what correlation existed between the Paddle and Basket Method dissolution results; what was relevant was whether or not the prior art composition in fact would, if tested using the Paddle Method, give a dissolution value in the 15–50% range.

which disclosed a drug product containing that same active ingredient. Maloney did not, however, disclose that oxymorphone would produce the food effect. Nevertheless, the Federal Circuit affirmed the rejection because Maloney's failure to describe the inherent properties of oxymorphone did not change the fact that Maloney taught expressly to use oxymorphone in a pharmaceutical composition that would *in fact* exhibit the food effect (emphasis is again the Federal Circuit's):

> Substantial evidence supports the Board's finding, based upon the specification, which confirms that the claimed "food effect" is an inherent property of oxymorphone itself, present in both controlled release and immediate release formulations of that drug. This is not a case where the Board relied on an unknown property for a *teaching*. Rather, Maloney's express teachings render the claimed controlled release oxymorphone formulation obvious, and the claimed "food effect" adds nothing of patentable significance.

Id. at 1070 (citations omitted).

Similarly here, it did not matter for overcoming the obviousness rejection whether the skilled artisan would have *appreciated* from Nyström that MCC was a mucoadhesive; what mattered as indicated in the examiner's rejection was whether MCC was *in fact* a mucoadhesive. This is because Nyström contained an express teaching to combine an ordered mixture and MCC.[7] Orexo's non-italicized sentences sought to explain why this teaching in Nyström did not render the claimed invention unpatentable—namely, because MCC was, in fact, not a mucoadhesive agent for purposes of the '910 patent. Thus, Orexo's rationalization that "skilled persons would understand that applicant's statement…is based on the fact that Nyström does not address whether any of the materials listed therein exhibited bioadhesive properties" is inconsistent with the argument Orexo actually made to the examiner.

The second problem with Orexo's revisionist interpretation of the italicized statement "[i]n fact, NYSTROM fails to disclose or suggest a combination of ordered mixtures and

[7] *See, e.g.*, Nyström, col. 6, line 62 (referring to including Avicel® PH 101 in the ordered mixture). Avicel® was the trade name for MCC. Koutsoubas Opening Decl., Ex. 2 at ORM0000042 (referring to "microcrystalline cellulose (Avicel®)").

mucoadhesive agents," is that the statement is most reasonably read as going beyond MCC. This is because the term "mucoadhesive agents" is plural. Even though the examiner's rejection referred to MCC as the mucoadhesive disclosed by Nyström, Orexo did *not* respond to the rejection by saying "Nyström fails to disclose or suggest a combination of ordered mixtures *and MCC as a mucoadhesive agent*." Rather, Orexo's use of the plural could only reasonably be understood as broader than MCC, encompassing at the very least another material called out (as a disintegrant) in the examiner's rejection as being disclosed in Nyström, namely, cross-linked PVP. That broader statement would have been deceptively false if cross-linked PVP was, in fact, a mucoadhesive agent for purposes of the '910 patent, because Nyström taught (again as the examiner recognized in his rejection) a combination of ordered mixture and cross-linked PVP.

Orexo tries to make much of a tangential issue that was addressed in Mylan's Opening Brief at page 10 n. 8. Orexo argues in effect that because Orexo's representation to the patent examiner, if read literally, is untrue (inasmuch as it was contradicted by a material not mentioned in the rejection named Ac-Di-Sol), the representation should not be read literally. *See* OB 12–13. Orexo's argument "reduces to a request for a mulligan that would erase from the prosecution history the inventor's disavowal of a particular aspect of a claim term's meaning. Such an argument is inimical to the public notice function provided by the prosecution history." *Hockerson-Halberstadt, Inc. v. Avia Group Int'l, Inc.*, 222 F.3d 951, 957 (Fed. Cir. 2000).[8]

Orexo is using Ac-Di-Sol as a classic straw man, but it is actually useful as contrast, because the intrinsic evidence concerning Ac-Di-Sol and cross-linked PVP is so different. Unlike

[8] Orexo has not shown that a reasonable competitor would have known that the statement made in the prosecution history was erroneous insofar as the materials described in the rejection were concerned. Rather, Dr. Peppas merely restates Orexo's position that the remarks referred to "the fact that…Nyström does not address whether any of the materials listed were bioadhesive" and merely points to the disclosure of Ac-Di-Sol in Nyström as support for that assertion. Peppas Decl., ¶ 142. *See also* Peppas Decl. ¶ 143 ("Nyström EP 725 does not address whether any material possesses bioadhesive properties. The list of disintegrants in Nyström EP 725 without further information regarding properties does not assist in determining what should and should not be included within the meaning of 'bioadhesion and/or mucoadhesion promoting agent' in the '910 patent.")

cross-linked PVP, Ac-Di-Sol was not specifically named in the examiner's rejection, and thus one would not necessarily assume that the statement encompassed a material not specifically mentioned in the rejection. *See generally In re Wiechert*, 370 F.2d 927, 933 (C.C.P.A 1967) ("An applicant's attention and response are naturally focused on that portion of the reference which is specifically pointed out by the examiner.")[9] Moreover, the statement "Nyström fails to disclose or suggest a combination of ordered mixtures and mucoadhesive agents," is only one piece (albeit an important piece) of intrinsic evidence, and other intrinsic evidence specific to Ac-Di-Sol is inconsistent with the general statement (*e.g.*, the description of Ac-Di-Sol as a mucoadhesive in the '910 patent at col. 5, lines 42–43). The failure to specifically name Ac-Di-Sol in the rejection coupled with the other intrinsic evidence, might well foreclose prosecution disavowal for Ac-Di-Sol. *See generally Computer Docking Station Corp. v. Dell, Inc.*, 519 F.3d 1366, 1374–75 (Fed. Cir. 2008) (prosecution disavowal must be unambiguous).

There is no such ambiguity for cross-linked PVP, because there is no intrinsic evidence to undermine the plain import of the disclamatory statement that "Nyström fails to disclose or suggest a combination of ordered mixtures and mucoadhesive agents." Indeed, all of the intrinsic evidence points to the conclusion that inasmuch as MCC is not a mucoadhesive for purposes of the '910 patent, then neither is cross-linked PVP.

II. "ESSENTIALLY WATER-FREE" IN THE '910 PATENT HAS THE SAME MEANING AS "ESSENTIALLY WATER-FREE" IN THE PRIOR ART NYSTRÖM REFERENCE

Mylan's proposed construction of "essentially water-free" has consistently included the requirement that "[n]o water is intentionally added during the manufacturing process."[10] The distinction between water intentionally added and water inadvertently (for lack of a better word)

[9] As the Court is probably already aware, the Court of Customs and Patent Appeals, the CCPA, was a predecessor to the U.S. Court of Appeals for the Federal Circuit. *South Corp. v. United States*, 690 F.2d 1368, 1369 (Fed. Cir. 1982) (en banc).

[10] Orexo criticizes Mylan for alleged changes in Mylan's construction of this term, but as explained at the end of this section, the essence of Mylan's construction has been unchanged.

added, is well understood by Orexo and its expert: "Skilled persons would understand that water may be used during manufacture (*whether introduced intentionally* or through excipients or the active ingredient), and small amounts of water may be present in the final product." OB at 8 (emphasis added). *See also* Peppas Dep. at 22:11–23:3.

There is no dispute that for the '910 patent "[i]t is preferred to formulate the composition according to the invention by use of the technology for formulating rapidly dissolving ordered-mixture compositions disclosed in European patent EP 0324 725 [Nyström]." '910 patent, col. 3, lines 26–29). Likewise, there is no dispute that the term "essentially water-free," as used in Nyström, means that the intention is to exclude water. This is the testimony of Orexo's expert:

> Q: What is the meaning of "essentially water free" in the Nystrom reference?
>
> A: The intention of the inventors was to exclude water to prevent probably prevent [sic] early dissolution of the drug.

Peppas Dep. 78:14–20.

Orexo asserts that "Mylan cannot rely on the disclosure from Nyström to construe 'essentially water-free' because the '910 patent passage addressing 'essentially free from water' is very different from the passage in Nyström," and Orexo then puts the respective passages side-by-side with the differences between the passages in bold. OB at 6. With this use of emphasis, Orexo would obscure the essential point that both the '910 patent and Nyström taught that the presence of water results in premature—and thus undesirable—dissolution of the active substance. Orexo's own expert, however, prepared a side-by-side comparison of the passages from the '910 patent and Nyström, and applied different emphasis in the form of underlining. This underlining highlighted the common importance of avoiding premature dissolution of the active substance:

'910 Patent Col. 7, lines 36–43	Nyström Patent (EP 725) Col. 4, lines 65–Col. 5, line 4
Irrespective of the form given to the preparation, it is important that the preparation is essentially free from water, ***since its bio/mucoadhesion promoting character results from its practically instantaneous hydration when we brought into contact with water or saliva. Premature hydration would drastically decrease the mucoadhesion promoting properties*** and result in a premature dissolution of the active substance.	Irrespective of the form given to the preparation, it is important that the preparation is essentially free from water, since the presence of water would result in premature dissolution of the active substance.

Peppas Decl. ¶ 40 (emphasis in original)

Orexo's expert was asked about the underlining, and he testified as follows in his deposition:

> Q: Could you turn to paragraph 40 of your declaration, and the surrounding paragraphs that relate to that. Paragraph 40 of your declaration, you have a side-by-side comparison of a portion of the Nystrom reference and a portion of the '910 Patent that brings us here today, correct?
>
> A: Yes, sir.
>
> Q: The sentence that you quote from Nystrom says, and let me read it, "Irrespective of the form given to the preparation, it is important that the preparation is essentially free from water, since the presence of water would result in premature dissolution of the active substance." Did I read that correctly?
>
> A: Yes, I see that.
>
> Q: And did you also emphasize in your declaration the words "premature dissolution of the active substance"?
>
> A: Yes, sir.
>
> Q: So would you explain to me the—your understanding of mechanism of dissolution of the active substance that's described in Nystrom?

> Mr. Zullow: Objection. Mischaracterizes the whole purpose of paragraph 40.
>
> A: My inclusion of paragraph 40 and paragraphs around it is to explain the significant difference of the European application EP725 and the '910, and the presence of the mucoadhesive system. That is really the purpose of it. *The idea of the premature dissolution of the active substance remains in both systems. That is really what I am describing here.*
>
> Q: *Water will result in the premature dissolution of the active substance, right?*
>
> A: *Yes, it will.*
>
> Q: And so in addition, you're saying that the '910 Patent is also concerned about the effect of the exposure of water to the bioadhesive; is that correct?
>
> A: To the functional characteristics of the bioadhesives, yes.

Peppas Dep. 72:13–74:14 (emphasis added).

Not only is there nothing to suggest that the active substance in the putative invention of the '910 patent is *less* susceptible to dissolution in water than Nyström's invention, but the limited intrinsic evidence on the point is actually otherwise. The examiner understood from the '910 patent specification that "[t]he most important aspect of the invention is the fact that the compound remains water-free so that the active agents do not dissolve too quickly." Koutsoubas Opening Decl., Ex. 2 at ORM_00000160 (Sept. 26, 2002 Office Action at p. 5); *see also id.* at ORM_00000191 (May 19, 2003 Office Action at p. 3). The examiner's understanding makes particular sense because the putative invention of the '910 patent is directed to sublingual formulations where only a minute amount of water (saliva) would be available to dissolve the active substance rapidly, while Nyström involved compositions that were swallowed, and thus much more water is available (in the stomach) to dissolve the active substance. Thus, in *order to work, the active substance in the '910 patent's composition must be at least as sensitive to dissolution in water as that of Nyström.*

This distinguishes case law upon which Orexo relies for the proposition that Mylan's proposed construction improperly reads a process limitation into a claim for a composition.[11] Here the essential characteristics of the claimed invention require a manufacturing process that excludes water. The '910 patent specification, like the Nyström reference, expressly states that "it is important that the preparation is essentially free of water." '910 patent, col. 7, lines 36–38. And with good reason: an ordered mixture of active agent adhered to the surface of highly water soluble carrier particles is destroyed when it is exposed to water, because the whole purpose of the ordered mixture is to permit the active agent to dissolve quickly upon exposure to water. Thus, the manufacturing process for such an ordered mixture must avoid water, lest the process destroy the very thing it is trying to make. *See* Expert Declaration of Edmund J. Elder, Jr., Ph.D., R.Ph. ("Elder Decl.") ¶¶ 27, 33, Oct. 5, 2012, ECF No. 95-6 (use of dry mixing of active agent and carrier particles is necessary in forming ordered mixture, among other reasons, because the use of water during the manufacturing process has the potential to dissolve the "readily dissolvable" carrier particles).

Where, as here, the process of manufacture is integral to the performance of the final product, the process required to produce the claimed composition is properly incorporated into the definition of the composition:

> It is generally true, as Andersen argues, that product claims are not limited to the methods of manufacture disclosed in the specification and that the method of manufacturing, even when

[11] Orexo cites *Astra Aktiebolag v. Andrx Pharms., Inc*., 222 F. Supp. 2d 423, 469 (S.D.N.Y. 2002), *aff'd* 84 F. App'x 76, 80 (Fed. Cir. 2003), citing *Vanguard Prods. Corp. v. Parker Hannifin Corp*., 234 F.3d 1370, 1372–73 (Fed. Cir. 2000) (divided panel). In these cases, the patent application was examined without reference to the process by which the claimed product was made. Here, by contrast, the Nyström process was defined as the preferred way of making the product, the patent disclosed only processes avoiding water for making the claimed composition, and (as noted in the text) the examiner expressed his view that "[t]he most important aspect of the invention is the fact that the compound *remains* water-free so that the active agents do not dissolve too quickly." Koutsoubas Opening Decl., Ex. 2 at ORM_00000160 (Sept. 26, 2002 Office Action at p. 5) (emphasis added); *see also id.* at ORM_00000191 (May 19, 2003 Office Action at p. 3). "Remains water-free" implies a water-free process—namely, a product that when made is essentially water-free, and remains that way.

> cited as advantageous, does not of itself convert product claims into claims limited to a particular process. A novel product that meets the criteria of patentability is not limited to the process by which it was made. *However, process steps can be treated as part of a product claim if the patentee has made clear that the process steps are an essential part of the claimed invention.*

Andersen Corp. v. Fiber Composites, LLC 474 F.3d 1361, 1375 (Fed. Cir. 2007) (emphasis added; citation and internal quotation marks omitted).

The close similarity between the putative inventions of Nyström and the '910 patent supports the conclusion that "essentially water-free" means the same thing in both—water cannot be intentionally added during the manufacturing process. As Dr. Elder's declaration helps explain (Paragraphs 26–27 and 33–34), intrinsic evidence shows that no water should be intentionally added during the manufacturing process. Otherwise, the addition of water risks prematurely dissolving the active ingredient and the carrier particles, thereby disrupting the ordered mixture of active ingredient on the carrier particle surface, as well as prematurely hydrating the mucoadhesive.

Although "ordered mixture" is not a limitation of the second independent claim, claim 19, the term "essentially water-free" in that claim likewise connotes no intended addition of water at least because added water thwarts the requirement of claim 19 for "an effective amount of at least one pharmaceutically active agent in the form of microparticles adhered to the surfaces of carrier particles." Added water risks dissolving the highly soluble carrier particles and thus interfering with assembling the active agent on the surface of the carrier particles. *See* Elder Decl. ¶¶ 26–27. Moreover, the same claim term is presumed to have the same meaning throughout a patent, e.*g.*, *Phillips*, 415 F.3d at 1314, and indeed Orexo's own expert agrees that "essentially water-free" has the same meaning in both claims. Peppas Dep. 79:21–24 ("Q. Do you understand the term "essentially water free" to have the same meaning in Claim 1 and Claim 19? A. Yes, I do."). Accordingly, inasmuch (as explained above) "essentially water-free" means for claim 1 that there is no intentionally added water during the manufacturing process, "essentially water-free" also has the same meaning for claim 19.

Before moving on to the next claim term, Mylan would like to address Orexo's misleading assertion that Mylan changed its proposed construction of "essentially water-free" "no less than four times." The four iterations are listed below with emphasis added to show that essence of the proposed construction has not changed:

Iteration	Mylan's Proposed Construction
1. Draft Proposed Construction Rule 4.2 Disclosure	1. The ordered mixture contains so little water that there is no premature hydration of the bioadhesion and/or mucoadhesion promoting agent. *To avoid this hydration, no water may be added during the manufacture of the ordered mixture.*
2. Proposal Made During Negotiations About Claim Terms	2. *No water is intentionally added during the manufacturing process.*
3. Original Joint Claim Construction and Prehearing Statement	3. The ordered mixture contains so little water that there is no premature hydration of the bioadhesion and/or mucoadhesion promoting agent. *No water is intentionally added during the manufacturing process*.
4. Revised Joint Claim Construction and Prehearing Statement	4. *No water is intentionally added during the manufacturing process.*

Mylan's current proposed construction—that no water is intentionally added during the manufacturing process—has always been a component of its proposals. During the negotiations between counsel about the competing drafts of proposed claim terms, Mylan proposed Iteration #2 that crystallized the dispute between the parties and encompassed both claims where "essentially water-free" was a limitation (as noted above, in claim 1, "essentially water-free" modifies "ordered mixture," while in claim 19 the term modifies "pharmaceutical composition;" Iteration #2 made Mylan's construction applicable to both claims by changing "during the manufacture of the ordered mixture" to the more general "during the manufacturing process"). Orexo rejected Iteration #2, later criticized Mylan for Iteration #3, (that was closer to Iteration #1) and then when Mylan returned to Iteration #2 (Iteration #2 and #4 are identical), now

criticizes that iteration as well. The bottom line, however, is that Orexo cannot fairly deny that the essential dispute—Does the limitation encompass the intentional addition of water during the manufacturing process? —has been clear from the beginning. So too, as explained above, is the answer.

III. "MICROPARTICLES OF AT LEAST ONE PHARMACEUTICALLY ACTIVE AGENT" ARE A NECESSARY COMPONENT OF THE "ORDERED MIXTURE" IN CLAIM 1

Central to the parties' dispute about the meaning of "ordered mixture" is the dispute over whether the active agent is a necessary component of the mixture. Orexo says "no." See *e.g.*, OB at 23 ("For example, the active agent *may* but is not required to be the part of the 'ordered mixture.'") (emphasis in original).

The plain language of claim 1, as shown on page 18 of our opening brief, leaves no room for reasonable debate that the active agent *is* necessarily part of the ordered mixture:

> 1. A pharmaceutical composition for the treatment of acute disorders by sublingual administration, comprising an essentially water free, *ordered mixture of microparticles of at least one pharmaceutically active agent adhered to the surfaces of carrier particles*, said particles being substantially larger then send microparticles and being water-soluble, and a bioadhesion and/or mucoadhesion promoting agent mainly adhered to the surfaces of the carrier particles. (emphasis added)

Orexo misreads the patent specification as describing an embodiment where the bioadhesive replaces the active ingredient:

> In this embodiment, the bio/mucoadhesion promoting agent takes the place of the active agent in the ordered mixture describes in Nyström: "Thus, the bio/mucoadhesion promoting agent is admixed in the same way as the active compound described in European patent 0 324 725." (*See* col. 5, ll. 53–65). This passage expressly teaches that the active agent in the Nyström prior [sic; art] should *be replaced* with the bio/mucoadhesive promoting agent, resulting in an "ordered mixture" of the bio/mucoadhesion promoting agent and carrier.

OB at 23 (emphasis in original).

Orexo's construction makes no sense in light of the rest of the patent specification. The invention is directed to a sublingual tablet to treat an acute disorder by administering *an active agent* contained in an ordered mixture. Administering a mucoadhesive does not treat an acute disorder.

The specification excerpt cited by Orexo is actually describing what is depicted in both Example 1 and Example 2 of the '910 patent, examples which are expressly described as illustrating the preferred embodiments. *See* '910 patent: col. 7, lines 65–67. In those examples, as Orexo's expert recognized, the active agent is part of the ordered mixture. Peppas Dep. 153:10–13.

The original foreign patent application related to the '910 patent was filed in 1998, but Orexo quotes from an article published five years later at page 24 of its brief. That later-published article suggests that an ordered mixture could be created by mixing carrier particles and muco/bioadhesive, but that suggestion does not address—let alone answer—the question of whether the ordered mixture *of claim 1* requires the presence of the active agent. As Orexo puts it (quoting that late-published article, with the emphasis added by Orexo): "It is then theoretically possible to add the active substance to the surface of these carrier particles, resulting in *ordered units comprising coarse particles carrying both bioadhesive component and drug*." OB at 24 (emphasis in original) (quoting Peppas Decl., Ex. 16). Whether or not that statement is true, the statement in no way contradicts the plain language of the claim, and the teaching of the '910 patent specification (when read in full, including the examples), that the ordered mixture of claim 1 must include the active agent in addition to the possible inclusion of mucoadhesive agent. *See* Mylan's Opening Br. at 17–19.

Once the predicate is established that the active agent is a necessary component of the ordered mixture, then one can more readily see the integrated nature of the claim limitation: "ordered mixture of microparticles of as least one pharmaceutically active agent adhered to the surfaces of carrier particles, said particles being substantially larger than said microparticles and being water-soluble." As explained in our opening brief, the carrier particles must be

substantially larger than the microparticles of active agent so that the microparticles bind to the carrier particles. *Id.* at 16–17. Since the microparticles, as exemplified in the patent specification, are 24 microns or smaller, the carrier particles must then be "substantially larger" than 24 microns. The microparticles in turn (as taught in the Nyström prior art reference) "adhere or bind to the surfaces of the larger carrier particles." Nyström, col. 1, lines 21–22. Thus, the integrated limitation is properly construed as:

> A mixture of carrier particles and adherent microparticles of the active pharmaceutical agent wherein:
>
> 1) the microparticles of the active agent have a particle size no greater than about 24 microns,
>
> 2) the carrier particles are water soluble and substantially greater than 24 microns; and
>
> 3) the microparticles bind to the surfaces of the carrier particles.

The *Phillips* court approvingly quoted this excerpt from one of its earlier opinions:

> Ultimately, the interpretation to be given a term can only be determined and confirmed with a full understanding of *what the inventors actually invented* and intended to envelop with the claim. The construction that stays true to the claim language and most naturally aligns with *the patent's description of the invention* will be, in the end, the correct construction.

Phillips, 415 F.3d at 1316 (emphasis added; citation omitted).

This excerpt helps explain what is wrong with several of Orexo's arguments related to the ordered mixture limitation (and other limitations, for that matter). What the inventors purported to invent, as described in the patent's summary of the invention, was a sublingual dosage form comprising an "essentially water-free" ordered mixture of active agent microparticles on carrier particles that also have mucoadhesive mainly adhered to the surface. In such an ordered mixture, as explained in the preceding section, the adherence of the smaller particles of active agent to the larger carrier particles occurs in a process that excludes water because the sublingual dosage

form is designed to quickly dissolve upon exposure to a tiny amount of water. *See* '910 patent, col. 3, lines 35–50.

Orexo argues that Mylan is trying to limit Orexo to the preferred embodiments of its invention, but instead Mylan is arguing for limiting the claim to what the inventors actually invented based on the patent's description of the invention. This is nicely illustrated by Orexo's complaint that Mylan would restrict the particles of active agent based on the following statement in the '910 patent: "The particles of fentanyl or salt thereof will suitably have a maximum particle size of about 24 µm but will preferably not be greater than 10 µm." (col. 7, lines 7–9). Orexo argues that the 24µm/10µm values are limited to the specific active ingredient (fentanyl), but Orexo overlooks that the inventors' own description of what they invented has a general particle size limitation:

> The possibility to use ordered mixtures for sublingual administration, where the volume of liquid is available as solvent is limited to a few milliliters, has not been considered as a feasible approach. It was therefore unexpected that the present form of a solid dosage form preparation and administration route gives positive and useful results. In such an ordered mixture, *the active agent or agents have a mean particle size below 10 µm.*

'910 patent at 3:44–52 (emphasis added)

As noted in our opening brief (page 16 n.11), the upper limit on the particle size of the active agent might even be described more restrictively based on the foregoing as 10 µm rather than 24 µm, and Mylan would be happy with either size limitation. The important point is that an appreciation of what the inventors actually purported to invent leads to an understanding that the "ordered mixture" is part of an integrated limitation requiring, *inter alia*, adherence to substantially larger carrier particles by active agent microparticles that are no bigger than 24 microns.

IV. "TREATMENT" IS NOT A HOPELESS GENERALITY

Turning now to claim 19, the plain language of the claim leaves open only one definition of "effective amount"—an amount that is effective to accomplish the stated purpose of the claimed method, namely "the treatment of acute disorders:"

> 19. *A method for the treatment of acute disorders*, wherein to an individual affected with said disorder is administered sublingually at least one dose unit of an essentially water-free pharmaceutical composition containing an *effective amount* of at least one pharmaceutically active agent…(emphasis added).

Thus, the key to the meaning of "effective amount" is the meaning of "treatment," and here the Court is presented with two variant options by the parties. Orexo offers a definition ("[t]he application of medicines, surgery, psychotherapy, etc. to a patient or to a disease or symptom") that leads to "effective amount" having no meaning, because administration of *any* amount would qualify as "the application of medicines…to a patient or to a disease or symptom." By contrast, Mylan's proposed definition ("control") does provide meaning, meaning that has the added virtue of being taken directly from the patent specification.

On the substance, there is only one real choice to make between the two proferred constructions of "treatment." Mylan's proposed construction provides meaning to "effective amount" and is taken directly from the intrinsic evidence. Orexo's proposed construction does neither, and thus is unworthy of acceptance by the Court under controlling legal principles that give preeminent weight to intrinsic evidence, *see Phillips*, 415 F.3d at 1311–19, and favor constructions giving meaning to all claim terms, *see Bicon Inc. v. Straumann Co.*, 441 F.3d 945, 950 (Fed. Cir. 2006) ("claims are interpreted with an eye toward giving effect to all terms in the claim").

Orexo complains without basis that "in violation of the local rules, Mylan changed its construction to 'control'." OB at 28–29. There was no violation of the local rules. In the midst of a meet-and-confer process about the draft claim constructions—a process, we would add proudly, that removed about a dozen claim terms from the original list of disputed terms requiring court resolution—Mylan proposed "control" as a definition of "treatment" that

crystallized the dispute between the parties. As the meet-and-confer illuminated, Mylan's original proposed construction had potential to create unresolved ambiguity even after the Markman proceeding, because that draft construction—which was "relieving a medical condition"—could be understood as *partial* relief or *total* relief. Rather than asking the Court later to "construe the construction," *Semiconductor Energy Lab Co., Ltd. v. Chi Mei Optoelectronics Corp.*, 2006 WL 6130994, at *6 (N.D. Cal. Mar. 27, 2006) (Patel, J.), Mylan gave notice during the meet-and-confer of a revised proposed definition of "treatment" as "control", which resolved the ambiguity so that the Court would need construe "treatment" only once.

CONCLUSION

The intrinsic evidence supports Mylan's proposed interpretations of the disputed claim terms. For this and the other reasons described both above and in the opening brief, Mylan asks the Court to adopt Mylan's proposed constructions.

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Respectfully submitted,

By: s/ Arnold B. Calmann

Arnold B. Calmann (abc@saiber.com)
Jeffrey Soos (js@saiber.com)
Katherine A. Escanlar (kae@saiber.com)
SAIBER LLC
One Gateway Center, 10th Floor
Newark, New Jersey 07102-5311
973-622-3333
973-286-2465 (facsimile)

Douglass C. Hochstetler
(DHochstetler@KelleyDrye.com)
Constantine Koutsoubas
(CKoutsoubas@KelleyDrye.com)
KELLEY DRYE & WARREN LLP
333 West Wacker Drive
26th Floor
Chicago, IL 60606
312-857-7070

312-857-7095 (facsimile)

Beth D. Jacob (BJacob@KelleyDrye.com)
Sung W. Kim (SuKim@KelleyDrye.com)
KELLEY DRYE & WARREN LLP
101 Park Avenue
Suite 1700
New York, NY 10178
212-808-7800
212-808-7897 (facsimile)

Attorneys for Defendants/Counterclaim Plaintiffs Mylan Pharmaceuticals Inc. and Mylan Inc.